18. (Reiterated.) The method of claim 17, wherein before hybridization, the nucleic acid material of the biological sample is amplified by the polymerase chain reaction.

19. (Reiterated.) A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising:

a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions; and

b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds the polypeptide of claim 1.

20. (Reiterated.) A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1; and

b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound; and

c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a deviation between the activities is indicative of a compound that modulates the activity of the polypeptide of claim 1.

REMARKS

Applicants' invention is directed to a polypeptide having strong homology to type II integral membrane proteins in humans (IMP-2), and compositions containing them, which have a variety of utilities, in particular in expression profiling (see the specification, e.g., at pages 37-38), and in particular for diagnosis of conditions or diseases characterized by expression of IMP-2, for toxicology testing and for drug discovery. The polypeptide has chemical and structural homology with the mouse E25AMM protein (GI 624778; SEQ ID NO:3) (Deleersnijder,W. et al. (1996) J. Biol. Chem. 271:19475-19482). In particular, IMP-2 and E25AMM share 39.8% identity overall and 49% identity and 71% similarity over the carboxy-terminal domains

(residues 115-265 of IMP-2 and residues 111-261 of E25AMM). Figure 2 provides an alignment between the amino acid sequences of SEQ ID NOS:1 and 3 (see specification pages 14-15).

The invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Fig. 1. IMP-2 is 266 amino acids in length and contains nine cysteine residues (i.e., C_{38}, C_{54}, C_{56}, C_{57}, C_{89}, C_{164}, C_{223}, C_{248}, and C_{265}). In addition to providing sites for disulfide bond formation, the cysteine residues provide potential sites for palmitoylation. Five of the nine cysteine residues found in human IMP-2 are conserved in location with cysteine residues found in the mouse E25AMM protein (i.e., C_{56}, C_{164}, C_{223}, C_{248}, and C_{265} of IMP-2). The human IMP-2 of the present invention contains numerous potential O-linked glycosylation sites (*i.e.*, serine and threonine residues). IMP-2 has a single potential N-linked glycoslyation site (*i.e.*, Asn-X-Ser/Thr) (*i.e.*, N_{170}) which is conserved in location with the single N-linked glycoslyation site found in the mouse E25AMM protein (Deleersnijder et al., supra). In addition, the human IMP-2 of the present invention contains numerous potential phosphorylation sites (*i.e.*, typically the hydroxyl groups of serine, threonine and tyrosine residues although asparagine, histidine and lysine residues may also be phosphorylated), including a potential site for phosphorylation by cAMP-dependent protein kinase (*e.g.*, R-X-S/T) (*i.e.*, T_{236}) (specification page 14, lines 6-20).

The IMP-2 protein of the present invention, like the mouse E25AMM protein, has an acidic isoelectric point (pI) (IMP-2 has a pI of 4.86 and E25AMM has a pI of 5.41). In addition, the IMP-2 protein of the present invention, like the mouse E25AMM protein, has a high content of leucine and isoleucine residues (IMP-2 contains 9% leucine and 9% isoleucine; E25AMM contains 10.2% leucine and 8% isoleucine). IMP-2 contains a stretch of hydrophobic amino acid residues at positions 53-76 which presumably forms the membrane spanning domain. As illustrated by Figs. 3 and 4, IMP-2 and E25AMM have similar hydrophobicity plots (specification page 14.).

R. Vidal et al. (1999) Nature 399:776-781 disclose a polynucleotide sequence identified as an integral transmembrane protein. The Vidal et al. protein has 100% similarity over 266 amino acids with SEQ ID NO:1 which further establishes SEQ ID NO:1 as an integral membrane protein. Vidal et al. describe their integral transmembrane protein as also having 9 cysteine residues and being rich in leucine and isoleucine residues, a transmembrane-spanning domain between amino acids 52 and 74, and a potential N-glycosylation site at asparagine 170. Furthermore, the Vidal et al. sequence was found to share homology with a mouse sequence (GI

624778) published by Deleersnijder et al. *supra* (GI624778).

Type II integral membrane proteins have a single transmembrane stretch of hydrophobic residues which is often located near the amino-terminus. The bulk of type II proteins comprises the carboxy-terminal domain which is located on the exterior side of the cell. The amino-terminal domain of type II proteins, located on the cytoplasmic side of the cell membrane, is typically small. Thus, the type II proteins generally lack enzymatically active domains on the cytoplasmic side of the membrane and thus are not themselves directly involved in transmembrane signaling. The carboxy-terminus of type II proteins typically comprises the active portion of the protein (e.g., the active site of an enzyme, the binding domain of a receptor) (specification pages 1-2).

The expression of the mouse *Itm2* gene (integral membrane protein 2) which encodes E25AMM, was found to be associated with chondro-osteogenic differentiation. The *Itm2* gene is strongly, although not exclusively, expressed in osteogenic tissue. In particular, *Itm2* is strongly expressed in mature osteoblasts and in early stages of secondary chondrogenesis. *Itm2* expression is not limited to chondro-osteogenic tissues as it is expressed in 1) heart, brain (choroid plexus), renal cortex, and the crypts of the small intestine (weak expression) and in 2) skin (stratum corneum), hair follicles and the acini of exocrine glands (strong expression) [Deleersnijder et al., *supra*].

Additional members of the E25 multigene family have been identified in the mouse and in humans. These additional E25 family members are expressed in a wide variety of tissues including adult and fetal brain, fetal liver, fetal spleen, lung, breast, placenta, prostate, adrenal gland, white blood cells and adult and fetal heart [Deleersnijder et al., *supra*] (specification pages 1-2.) Furthermore, Northern analysis (Fig. 5) shows the expression of the claimed IMP-2-encoding sequence in various libraries, at least 24% of which are cancerous or immortalized and at least 17% of which are involved with the immune response, including inflammatory and/or autoimmune disease (e.g., rheumatoid synovium, ulcerative colitis, Crohn's disease, primary biliary cirrhosis). Of particular note is the expression of IMP-2 mRNA in brain tumor (7/214), prostate tumor (6/214), breast tumor (3/214) and bladder tumor (3/214) libraries. This pattern of expression demonstrates that IMP-2 serves as a marker for cancerous cells, particularly brain and prostate tumor cells. In addition to its expression in a variety of tumors, IMP-2 is highly expressed in adult liver and fetal spleen and thus serves as a marker for these tissues (specification page 14.)

The rejection of claims 1 and 11 is improper, as the claims have a patentable utility as set forth in the instant specification, and a utility well-known to one of ordinary skill in the art.

Claims 1 and 11 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, based on the allegation that the claimed invention lacks patentable utility. The rejection alleges in particular that, "the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility . . . asserted utilities as set forth in the specification are considered to be general utilities that would be applicable to the broad class of the invention. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities." Because Applicant has not disclosed any specific and substantial utility for the claimed invention, credibility will not be assessed."

The invention at issue is a polypeptide sequence corresponding to a gene that is expressed in several specific tissues. Furthermore, as disclosed in the specification on page 15, lines 5-17, and lines 20-22:

> Northern analysis (Fig. 5) shows the expression of IMP-2-encoding sequences in various libraries, at least 24% of which are cancerous or immortalized and at least 17% of which are involved with the immune response, including inflammatory and/or autoimmune disease (e.g., rheumatoid synovium, ulcerative colitis, Crohn's disease, primary biliary cirrhosis). Of particular note is the expression of IMP-2 mRNA in brain tumor (7/214), prostate tumor (6/214), breast tumor (3/214) and bladder tumor (3/214) libraries. This pattern of expression demonstrates that IMP-2 serves as a marker for cancerous cells, particularly brain and prostate tumor cells. In addition to its expression in a variety of tumors, IMP-2 is highly expressed in adult liver and fetal spleen and thus serves as a marker for these tissues.
>
> As is demonstrated in Fig. 5, IMP-2 cDNA is strongly expressed in normal adult liver (>10% abundance; see LIVRNOT01 and LIVRNOM01 libraries) and its expression decreases precipitously in abnormal liver tissues, including primary biliary cirrhosis (see LIVRBCT01 library; 3.5% abundance) and liver tumors (see LIVRTUT01 library; 0.03% abundance) . . . A similar decrease in IMP-2 transcripts is observed when normal lung and lung tumors are compared; lung tumors show about a 50% decrease in IMP-2 transcript abundance as compared to normal adult lung (Fig. 5).

As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which necessarily require detailed knowledge of how the polypeptide coded for by the polynucleotide works. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Any of these uses meets the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph. Under these sections of the Patent Act, the patent applicant need only

show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.,* 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The rejection fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they

could be achieved. For these reasons alone the rejections should be overturned.

There is, however, an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999) and Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law. These inconsistencies are discussed separately below.

I. Use of the claimed polypeptide and a pharmaceutical composition characterized by expression of IMP-2 for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There is a "well-established" use for the claimed invention, there are specific practical and beneficial uses for the invention, and those uses are substantial. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling. Likewise, proteome expression profiling techniques have been developed in which the expression of numerous polypeptides is compared in two or more samples. Polypeptide or polypeptide fragments known to be expressed are tools essential to any technology that uses proteome expression profiling. See, *e.g.,* Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467 (2000).

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. One of these techniques is toxicology testing, which is used in both drug development and safety assessment. Toxicology testing is now standard

practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Genesis 24:153 (1999); Sandra Steiner and N. Leigh Anderson, *supra.*

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> ... for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, Environ. Health Perspec. 107(8):681 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening. This is true for both polynucleotides and polypeptides encoded by them.

There are numerous additional uses for the information made possible by expression profiling. Expression profiling is used to identify drug targets and characterize disease. See

Rockett et al., *supra*. It also is used in tissue profiling, developmental biology, disease staging, etc. There is simply no doubt that the sequences of expressed human genes all have practical, substantial and credible real-world utilities, at the very least for expression profiling.

Expression profiling technology is also used to identify drug targets and analyze disease at the molecular level, thus accelerating the drug development process. For example, expression profiling is useful for the elucidation of biochemical pathways, each pathway comprising a multitude of component polypeptides and thus providing a pool of potential drug targets. In this manner, expression profiling leads to the optimization of drug target identification and a comprehensive understanding of disease etiology and progression.

There is simply no doubt that the sequences of expressed human polynucleotides and polypeptides all have practical, substantial and credible real-world utilities, at the very least for biochemical pathway elucidation, drug target identification, and assessment of toxicity and treatment efficacy in the drug development process. Sandra Steiner and N. Leigh Anderson, *supra*, have elaborated on this topic as follows:

> The rapid progress in genomics and proteomics technologies creates a unique opportunity to dramatically improve the predictive power of safety assessment and to accelerate the drug development process. Application of gene and protein expression profiling promises to improve lead selection, resulting in the development of drug candidates with higher efficacy and lower toxicity. The identification of biologically relevant surrogate markers correlated with treatment efficacy and safety bears a great potential to optimize the monitoring of pre-clinical and clinical trials.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangier disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

B. The use of IMP-2 proteins for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

Even if, *arguendo*, toxicology testing, drug development and disease diagnosis (through expression profiling) are not well-established utilities (which expressly is <u>not</u> conceded), the claimed invention nonetheless has specific utility by virtue of its use in each of these techniques. There is no dispute that the claimed invention is in fact a useful tool in each of these techniques. That is sufficient to establish utility for both the polypeptide and the polynucleotides encoding it.

Nevertheless, the claimed invention is rejected on the grounds that it does not have a "specific utility" absent a detailed description of the actual function of the protein expressed by the claimed nucleic acid or identification of a "specific" disease it can be used to treat. Apparently relying on the Training Materials, the rejection is made based on a scientifically incorrect and legally unsupportable assertion that identification of the family or families of proteins to which the claimed invention belongs, without more, does not satisfy the utility requirement. None of these grounds is consistent with the law.

1. A patent applicant can specify a utility without any knowledge as to how or why the invention has that utility

It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortright*, 165 F.3d, at 1359 (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340 (Fed. Cir. 1989)). *See also Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570, 219 USPQ 1137 (Fed. Cir. 1983) ("[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests."). It follows that the patent applicant need not set forth the particular functionality of the claimed invention to satisfy the utility requirement.

Practical, beneficial use, not functionality, is at the core of the utility requirement. *Supra*

(introduction to § I). So long as the practical benefits are apparent from the invention without speculation, the requirement is satisfied. *Standard Oil Co. v. Montedison*, 664 F.2d 356, 374, 212 USPQ 327 (3d Cir. 1981); *see also Brana*, 51 F.3d at 1565. To state that a biological molecule might be useful to treat some unspecified disease is not, therefore a specific utility. *In re Kirk*, 376 F.2d 936, 945, 153 USPQ 48 (C.C.P.A. 1967). The molecule might be effective, and it might not.

However, unlike the synthetic molecules of *Kirk*, the claimed invention is known to be useful. It is not just a random sequence of speculative use. Because it is expressed in humans, a person of ordinary skill in the art would know how to use the claimed polynucleotide and/or polypeptide sequences -- without any guesswork -- in toxicology testing, drug development, and disease diagnosis regardless of how the polynucleotide or the protein it encodes actually functions. The claimed invention could be used, for example, in a toxicology test to determine whether a drug or toxin causes any change in the expression of integral membrane proteins. Similarly, the claimed invention could be used to determine whether a specific medical condition, such as cancer, affects the expression of type II integral membrane proteins and, perhaps in conjunction with other information, serve as a marker for or to assess the stage of a particular disease or condition.

In fact, the claimed polypeptide and/or polynucleotide sequences could be used in toxicology testing and diagnosis without **any** knowledge (although this is not the case here) of the protein for which it codes: it could serve, for example, as a marker of a toxic response, or, alternatively, if levels of the claimed polypeptide or polynucleotide remain unchanged during a toxic response, as a control in toxicology testing. Diagnosis of disease (or fingerprinting using expression profiles) can be achieved using arrays of numerous identifiable, expressed DNA sequences, or by two-dimensional gel analysis of the expressed proteins themselves, notwithstanding lack of any knowledge of the specific functions of the proteins they encode.

2. A patent applicant may specify a utility that applies to a broad class of inventions

The fact that the claimed invention is a member of a broad class (such as DNA sequences or the proteins they encode expressed in humans) that includes sequences other than those claimed that also have utilities in toxicology testing, drug discovery, disease diagnosis, etc. does not negate utility. Practical utilities can be directed to classes of inventions, irrespective of function, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. The law has

long assumed that inventions that achieve a practical use also achieved by other inventions satisfy the utility requirement. For example, many materials conduct electricity. Likewise, many different plastics can be used to form useful films. *Montedison*, 664 F.2d at 374-75; *Natta*, 480 F.2d at 1397. This is a general utility (practical films) that applies to a broad class of inventions (plastics) which satisfies the utility requirement of 35 U.S.C. § 101.

Not all broad classes of inventions are, by themselves, sufficient to inform a person of ordinary skill in the art of the practical utility for a member of the class. Some classes may indeed convey too little information to a person of ordinary skill in the art. These may include classes of inventions that include both useful and nonuseful members. *See In re Ziegler*, 992 F.2d 1197, 1201, 26 USPQ2d 1600 (Fed. Cir. 1993). In some of these cases, further experimentation would be required to determine whether or not a member of the class actually has a practical use. *Brenner*, 383 U.S. at 534-35.

The broad class of steroids identified in *Kirk* is just such a class. It includes natural steroids (concededly useful) and man-made steroids, some of which are useful and some of which are not. Indeed, only a small fraction of the members of this broad class of invention may be useful. Without additional information or further experimentation, a person of ordinary skill in the art would not know whether a member of the class falls into the useful category or not. This could also be the case for the broad class of "plastic-like" polypropylenes in *Ziegler*, which includes many -- perhaps predominately -- useless members.

The PTO routinely issues patents whose utility is based solely on the claimed inventions' membership in a class of useful things. The PTO presumably would issue a patent on a novel and nonobvious fishing rod notwithstanding the lack of any disclosure of the particular fish it might be used to catch. The standard being promulgated in the Guidelines and in particular as exemplified in the Training Materials, and being applied in the present rejection, would appear to warrant a rejection, however, on the grounds that the use of the fishing rod is applicable to the general class of devices used to catch fish.

The PTO must apply the same standard to the biotechnological arts that it applies to fields such as plastics and fishing equipment. *In re Gazave*, 379 F.2d 973, 977-78, 154 USPQ 92 (CCPA 1967) *quoting In re Chilowsky*, 299 F.2d 457, 461, 108 USPQ 321 (CCPA 1956) ("[T]he same principles should apply in determining operativeness and sufficiency of disclosure in applications relating to nuclear fission art as in other cases."); *see also In re Alappat*, 33 F.3d 1526, 1566, 31 USPQ2d 1545 (Fed. Cir. 1994) (Archer, C.J., concurring in part and dissenting in

part) ("Discoveries and inventions in the field of digital electronics are analyzed according to the aforementioned principles [concerning patentable subject matter] as any other subject matter."). Indeed, there are numerous classes of inventions in the biotechnological arts that satisfy the utility requirement.

Take, for example, the class of interleukins expressed in human cells of the immune system. Unlike the classes of steroids or plastic-like polypropylenes in *Kirk* and *Ziegler*, all of the members of this class have practical uses well beyond "throwaway" uses. All of them cause some physiological response (in cells of the immune system). All of the genes encoding them can be used for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular interleukin works. No additional experimentation would be required, therefore, to determine whether an interleukin has a practical use. It is well-known to persons of ordinary skill in the art that there is no such thing as a useless interleukin.

Because all of the interleukins, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there is no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given interleukin conveys a practical benefit or how that particular interleukin works.

Another example of a class that by itself conveys practical benefits is the G protein-coupled receptors ("GPCRs"). GPCRs are well-known as intracellular signaling mediators with diverse functions critical to complex organisms. They perform these functions by binding to and interacting with specific ligands. They are targets of many current drug treatments, including anti-depressants, anti-histamines, blood pressure regulators, and opiates.

Newly-identified GPCRs are used intensively in the real-world, even in cases where neither the specific ligand that binds to the GPCR or the precise biological function of the GPCR is known. Newly identified GPCRs are used, for example, as toxicity controls for drug candidates known to bind other GPCRs. Because a person of ordinary skill in the art would know how to use any GPCR to achieve a practical benefit, even without any detailed or particular knowledge as to how it works, GPCRs as a class meet the utility requirement.

In fact, **<u>all</u>** isolated and purified naturally-occurring polynucleotide and polypeptide sequences which are expressable (i.e., which are not pseudogenes that are never expressed during any natural biological process) can be and **are** used in a real-world context as tools for toxicological testing, e.g., for drug discovery purposes. This utility applies to all sequences actually

expressed, yet in each case, the utility of the sequence is quite specific, e.g., insofar as it is used to detect its own specific complementary sequence in a sample containing many different sequences.

Integral membrane proteins, like interleukins, GPCRs and fishing rods, is a class that by itself conveys practical benefits. Unlike steroids and "plastic-like" polypropylenes, the claimed integral membrane protein, is expressed by humans, and can be used as a tool for toxicology testing. The claimed invention could be used, for example to determine whether a drug candidate affects the expression of IMP-2 proteins in humans, how it does so, and to what extent. Just as there are no useless interleukins and GPCRs, there are no useless IMP-2 proteins. As these are practical, real-world uses, the application need not describe particular functionality or medical applications that would only supplement the utilities known to exist already.

C. Because the use of IMP-2 proteins in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

The claimed invention's use as a tool for toxicology testing is just such a practical, real-world use. The PTO nonetheless rejected the claims at issue on the ground that the use of an invention as tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. In fact, the PTO issues patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the <u>only</u> known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the CCPA held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would

confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include: assessing IMP-2 expression in the diagnosis of disease when compared to a normal or standard profile for IMP-2 expression (see specification page 15, lines 14-20) and the use of IMP-2, its catalytic or immunogenic fragments or oligopeptides thereof, can be used for screening libraries of compounds in any of a variety of drug screening techniques (specification page 41, lines 11-13).

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

II. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

In addition to alleging a "specific" use for the claimed subject matter, a patent applicant must present proof that the claimed subject matter is in fact useful. *Brana*, 51 F.3d at 1565-66. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326, 206 USPQ 885 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762.

A patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See Langer*, 503 F.2d at 1391-92. If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The Revised Guidelines are in agreement with this procedure. *See* Revised Interim Guidelines at ¶¶ 3-4.

The issue of proof often arises in the chemical and biotechnological arts when the patentee asserts a utility for a claimed chemical compound based on its homology or similarity to another compound having a known, established utility. In such cases, the applicant can demonstrate "substantial likelihood" of utility by demonstrating a "reasonable correlation" between the utility -- not the function -- of the known compound and the compound being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895 (Fed. Cir. 1996). Accordingly, under *Brana*, the Patent Office must accept the asserted utility unless it can show that a person of ordinary skill in the art would reasonably doubt that a "reasonable correlation" exists. If the Patent Office makes such a showing, however, the applicant may submit evidence in support of the correlation.

In the present case, the specification (pages 14-15) clearly discloses that the claimed IMP-2 has:

> the amino acid sequence of SEQ ID NO:1, as shown in Fig. 1. IMP-2 is 266 amino acids in length and contains nine cysteine residues (i.e., C_{38}, C_{54}, C_{56}, C_{57}, C_{89}, C_{164}, C_{223}, C_{248}, and C_{265}). In addition to providing sites for disulfide bond formation, the cysteine residues provide potential sites for palmitoylation. Five of the nine cysteine residues found in human IMP-2 are conserved in location with cysteine residues found in the mouse E25AMM protein (i.e., C_{56}, C_{164}, C_{223}, C_{248}, and C_{265} of IMP-2). The human IMP-2 of the present invention contains numerous potential O-linked glycosylation sites (*i.e.*, serine and threonine residues). IMP-2 has a single potential N-linked glycosylation site (*i.e.*, Asn-X-Ser/Thr) (*i.e.*, N_{170}) which is conserved in location with the single N-linked glycosylation site found in the mouse E25AMM protein (Deleersnijder et al., supra). In addition, the human IMP-2 of the present invention contains numerous potential phosphorylation sites (*i.e.*, typically the hydroxyl groups of serine, threonine and tyrosine residues although asparagine, histidine and lysine residues may also be phosphorylated), including a potential site for phosphorylation by cAMP-dependent protein kinase (*e.g.*, R-X-S/T) (*i.e.*, T_{236}).
>
> The IMP-2 protein of the present invention, like the mouse E25AMM protein, has an acidic isoelectric point (pI) (IMP-2 has a pI of 4.86 and E25AMM has a pI of 5.41). In addition, the IMP-2 protein of the present invention, like the mouse E25AMM protein, has a high content of leucine and isoleucine residues (IMP-2 contains 9% leucine and 9% isoleucine; E25AMM contains 10.2% leucine and 8% isoleucine).
>
> IMP-2 contains a stretch of hydrophobic amino acid residues at positions 53-76 which presumably forms the membrane spanning domain. As illustrated by Figs. 3 and 4, IMP-2 and E25AMM have similar hydrophobicity plots.
>
> IMP-2 has chemical and structural homology with the mouse E25AMM protein (GI 624778; SEQ ID NO:3) (Deleersnijder et al., supra). In particular, IMP-2 and E25AMM share 39.8% identity overall and 49% identity and 71% similarity over the carboxy-terminal domains (residues 115-265 of IMP-2 and residues 111-261 of E25AMM). A pair of residues are said to be similar if they represent conservative substitutions. Figure 2 provides an alignment between the amino acid sequences of SEQ ID NOS:1 and 3.

The only evidence of record shows that a person of ordinary skill in the art would not doubt that IMP-2 is in fact an integral membrane protein, which is known to have a specific utility.

By ignoring the "reasonable correlation" requirement in the case law and failing to illustrate the procedure established by *Brana*, the Examiner has failed to set forth a proper *prima facie* case, and the rejection does not shift the burden of proof to Applicants for rebuttal. In fact, the rejection must be withdrawn, as the Examiner has failed to meet PTO's burden in the first place of establishing a proper rejection. There is no proper rejection for Applicants to rebut.

To the extent that the rejection set forth in the Office Action on pages 4-5 as a rejection under 35 U.S.C. § 112, first paragraph, for lack of written description is based on the same

reasoning, Applicants submit that this rejection is inapt and in any case is overcome for the same reasons. Again, the poorly supported assertions and mischaracterizations in the Office Action fail to provide the requisite evidence or sound scientific reasoning sufficient to establish that one of ordinary skill in the art would be more likely than not to doubt the veracity of Applicants' asserted utility. The specification clearly provides a written description of the invention, as well as discloses how one of skill in the art can make and use it. One of ordinary skill in the art would be enabled by the teachings in the specification as well as the state of the art to find and identify sequences encompassed by the claims.

III. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000)("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible, "throw-away" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food" do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000)

(quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana*, *supra* (disclosure describing a claimed antitumor compound as homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus, the Training Materials cannot be applied consistently with the law.

IV. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

<u>Rejection under 35 USC § 102(b)</u>

Claims 1 and 11 are rejected under 35 USC § 102(b) as anticipated by Deleersnijder et al. The reject states that, " . . . Deleersnijder et al. teach biologically active fragments and immunological fragments of SEQ ID NO:1." Applicants respectfully bring to the Examiner's attention that the Deleersnijder et al. paper was published in the August 9, 1996 issue of the Journal of Biological Chemistry. Applicants further direct the Examiner's attention to the Transmittal in which Applicants claim priority to the earlier parent application, USSN 08/791,338, filed on January 31, 1997, less than one year after the Deleersnijder et al. paper. Therefore, the rejection under 35 USC § 102(b) is inapt.

However, if the Examiner had intended to apply 35 USC § 102(a), Applicants submit that a rejection under 35 USC § 102(a) is also overcome. Applicants define "fragments" as, "of about 15 amino acids or greater in length which define fragments unique . . . " (see specification page 3, line 3-4). Comparison of SEQ ID NO:1 (632664) and GI 624778 as shown in Figure 2 show no area of 15 consecutive amino acids or greater in length identical between the two sequences. Therefore, any possible rejection under 35 USC § 102(a) does not apply as there are no fragments unique within the Deleersnijder et al. sequence which are identical to 15 or greater consecutive amino acids in SEQ ID NO:1.

<u>(10) CONCLUSION</u>

Applicants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity" as set forth in the Office Action and as justified in the Revised Interim Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold

the facts and holdings of these prior cases, "like a nose of wax,"[1] to target rejections of claims to polypeptide and polynucleotide sequences where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

In light of the above amendment and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited. No new matter is added by any of these amendments.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650)855-0555.

A one month extension fee is due with this response. Please charge Deposit Account No. 09-0108 in the amount of $110.00 as set forth in the enclosed transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. 09-0108. This form is enclosed in duplicate.

Respectfully submitted,

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[1] "The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." *(Parker v. Flook,* 198 USPQ 193 (US SupCt 1978))